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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/914,615	12/26/2001	Paul Meers		9551

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EXAMINER

KISHORE, GOLLAMUDI S

ART UNIT	PAPER NUMBER
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1615

DATE MAILED: 03/16/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/914,615

Applicant(s)

MEERS ET AL.

Examiner

Gollamudi S Kishore, PhD

Art Unit

1615

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 29 January 2004.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-4 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-4 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 13) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.
- a) ☐ The translation of the foreign language provisional application has been received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

- ☐ Notice of References Cited (PTO-892)
- ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____
- ☐ Interview Summary (PTO-413) Paper No(s). _____
- ☐ Notice of Informal Patent Application (PTO-152)
- ☐ Other: _____

DETAILED ACTION

The amendment filed on 1-29-04 is acknowledged.

Claims included in the prosecution are 1-4.

Claim Rejections - 35 USC § 102

1. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless -

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

2. Claims 1, 3 and 4 are rejected under 35 U.S.C. 102(a) as being anticipated by Kim (5,723,147).

Kim discloses a process of preparation of liposomes in which the lipid in an organic solvent is added with an aqueous solution of an active agent, which in turn is added, with a second aqueous solution containing lysine. The organic solvent is then removed. Kim teaches various active agents including DNA and RNA (abstract, col. 6, line 62 and Examples). Instant claims do not recite specific complexing agents and the nature of complexing, i.e., whether it is ionic or covalent. Since anions and cations are known to interact to form complexes and since Kim teaches both anionic and cationic active agents (morphine, morphine sulfate and nucleic acids), they would naturally be complexing with lysine (free base) or lysine hydrochloride. The reference thus, meets the requirements of instant claims.

Art Unit: 1615

Applicant's arguments have been fully considered, but are not found to be persuasive. Applicant argues that Kim teaches the formation of inclusion complexes of water-soluble compounds with cyclodextrins and the encapsulation of the inclusion complex for controlled release and that Kim fails to disclose every element of the present invention. This argument is not found to be persuasive. First of all, the examiner is unable to find cyclodextrin anywhere in Example 1. Secondly, as pointed out before, Kim teaches the same steps of dissolving the lipid in an organic solvent, which is added with an aqueous solution of an active agent, which in turn is added, with a second aqueous solution containing lysine. The organic solvent is then removed. Kim teaches various active agents including DNA and RNA in Example 1. Even assuming that Kim contains cyclodextrin, instant claim language does not exclude this compound. With regard to applicant's argument that claim 1 requires that the complex is no greater in diameter than the diameter of the droplet, the examiner points out that in Kim the complex is within the droplet and therefore, the lesser diameter of the complex than the droplet is implicit. The rejection is maintained.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

3. Claims 1 is rejected under 35 U.S.C. 102(a) as being anticipated by Kim (Cancer Research 53, pp. 1596-1598, April 1993).

Kim discloses a process of preparation of liposomes in which the lipid in an organic solvent is added with an aqueous solution of an active agent, which in turn is added, with a second aqueous solution containing lysine. The organic solvent is then removed (Materials and Methods section on col. 2, page 1596).

Applicant's arguments have been fully considered, but are not found to be persuasive. Applicant's arguments are similar to those advanced for Kim, 147. Since the methodology in both Kim's references is the same, the same response as above is applicable.

Claim Rejections - 35 USC § 103

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

5. Claim 2 is rejected under 35 U.S.C. 103(a) as being unpatentable over Kim (5,723,147) cited above.

The teachings of Kim have been discussed above. Kim does not teach the addition of the complexing agent to the lipid solution first followed by the addition of the active agent solution. Since complexing occurs between the active agent and the complexing agent irrespective of which one is added first, instant method steps are deemed to be manipulatable steps practiced by an artisan.

Applicant's arguments have been fully considered, but are not found to be persuasive, Applicant argues that Kim is directed to multivesicular liposome system useful for providing prolonged and sustained in vivo exposure at a disease site of a therapeutic concentration of the biologically active substance and in contrast, the present invention provides methods which allow for the loading of bioactives into

Art Unit: 1615

liposomes at a high compound to lipid ratios. This argument is not found to be persuasive since motivation to use the method of Kim or modify the method of Kim need not be the same as applicant's. Furthermore, instant claim does not recite any lipid : compound ratios.

6. Claims 1-4 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kim (5,759,573).

Instant method claims are drawn to formation of liposomes wherein the active agent is complexed with a complexing agent; the method steps in claims 1 and 2 recite two variables. 1) the complexing agent is added in the second aqueous solution whereas the active agent is added in the first aqueous phase (claim 1); 2) the complexing agent is added in the first aqueous medium and the active agent is added in the second aqueous medium.

Kim discloses a process of preparation of liposomes in which the lipid in an organic solvent is added with an aqueous solution of an active agent, which in turn is added, with a second aqueous solution. The organic solvent is then removed. In Kim's process, the complexing agent, cyclodextrin is added in the first aqueous phase together with the active agent (col. 4, lines 13-26 and Example 1).

However, it would have been obvious to one of ordinary skill in the art to manipulate the basic process of preparation of liposomes, i.e., adding the complexing agent and the active agent together in the same aqueous medium with the expectation of obtaining liposomes with similar complexes because one of ordinary skill in the art would reasonably expect the complexation between the active agent and the

Art Unit: 1615

complexing agent to occur, irrespective of whether they are added together in the same phase or separately in two phases. Kim does not specifically teach the active agent to be a nucleic acid. However, in view of Kim's teachings that the method is applicable to any active agent, it is deemed obvious to one of ordinary skill in the art to use DNA or RNA as the active agent with a reasonable expectation of success.

Applicant's arguments have been fully considered, but are not found to be persuasive. Applicant's arguments are similar to those advanced for the other rejections over Kim's references. These have been addressed above. Applicant argues that Kim fails to disclose that the complex is no greater in diameter than the diameter of the water droplet. This argument is not found to be persuasive for the following reasons. As clearly evident from the example and the abstract of Kim, cyclodextrin is within the aqueous compartment of the liposomes. That means the water droplet is within the lipid bilayer and therefore, it is implicit that the cyclodextrin complex within the aqueous compartment (droplet) is lesser in diameter than the droplet itself.

1. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of

Art Unit: 1615

the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gollamudi S Kishore, PhD whose telephone number is (571) 272-0598. The examiner can normally be reached on 6:30 AM- 4 PM, alternate Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Thurman K Page can be reached on (571) 272-0602. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703 308 1234.



Gollamudi S Kishore, PhD
Primary Examiner
Art Unit 1615

GSK